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ARTICLE

Population pharmacokinetics of atacicept in systemic lupus erythematosus: An analysis of three clinical trials

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Abstract

B cell stimulating factor (BLyS) and a proliferation-inducing ligand (APRIL) are targets for novel treatments in patients with systemic lupus erythematosus (SLE). Atacicept is a recombinant, soluble fusion protein that blocks BLyS and APRIL activity. This study characterized the pharmacokinetic (PK) profile of atacicept using a population PK model and identified covariates explaining the PK variability. Total atacicept concentrations from a phase I study in healthy volunteers and two phase II studies in patients with SLE, using subcutaneous administration, were modeled using a quasi-steady-state approximation of the target-mediated drug disposition model with first-order absorption. The model included 3640 serum atacicept concentration records from 37 healthy volunteers and 503 patients with SLE and described total atacicept concentrations of the three trials, providing precise estimates of all parameters. Body weight and baseline BLyS concentration were the only statistically significant covariates, whereas no differences were found between patients and healthy volunteers. Apparent clearance and volume of the central compartment increased with body weight and initial target concentration increased with baseline BLyS. The change on atacicept exposure was moderate, with a difference in area under the curve compared with the median of 20%–32% for body weight, and 7%–18% for BLyS. Therefore, the effects of these covariates on atacicept exposure are not expected to be clinically relevant. The model described the complete total atacicept concentration–time profiles without finding any differences between healthy subjects and patients with SLE and supports the 150 mg once weekly dose for further trials.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Atacicept is a dual inhibitor of B-cell stimulating factor (BLyS) and a proliferation-inducing ligand that is currently under investigation. Clinical studies showed

Clinical trial registration numbers: EMR700461-022, NCT00624338, and NCT01972568.

that atacicept is well-tolerated and demonstrated improvements in measures of systematic lupus erythematosus (SLE) disease activity.

WHAT QUESTION DID THIS STUDY ADDRESS?

Using data from a phase I study in healthy volunteers and two phase II studies in patients with SLE, this study aimed to develop a population pharmacokinetic (PK) model to assess total serum concentrations of atacicept and identify covariates explaining PK variability.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The semimechanistic model described the complete total atacicept concentration–time profile in healthy subjects and patients with SLE following subcutaneous injection. Body weight and baseline BLyS concentration were the only statistically significant covariates, but their effects on atacicept exposure are not expected to be clinically relevant.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The modeling results, together with clinical efficacy and safety findings, will contribute to the identification of suitable doses of atacicept for further clinical development.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects several body systems and is characterized by a fluctuating disease course. Standard treatments, such as corticosteroids and immunosuppressive drugs, do not prevent unpredictable disease flares and progressive organ damage and are associated with considerable toxicities.[1,2] Such treatments have reached the limits of what they can achieve, and patients still die prematurely and/or have greatly impaired quality of life.[3] Novel treatments have therefore been sought, including biological agents that selectively target one or more immune system pathways.[4] Biologics are advantageous in that they target a specific molecule, therefore minimizing off-target adverse effects.

As B cells play an important role in the pathogenesis of autoimmune diseases,[5] factors involved in regulating B cell maturation, survival, and function are obvious targets. In particular, two circulating members of the tumor necrosis factor family, B-cell stimulating factor (BLyS; also called B cell-activating factor) and a proliferation-inducing ligand (APRIL), are overexpressed in several autoimmune diseases, including SLE.[6,7]

To date, only two biological drugs have been approved for the treatment of SLE: belimumab, a monoclonal antibody that inhibits BLyS,[8] and anifrolumab, a monoclonal antibody to type I interferon receptor subunit 1.[9] However, the proportion of patients who responded to these treatments in clinical trials was relatively low (42%–57%) and the treatment effect compared with placebo was modest.[8–10] Atacicept is a novel, fully human, recombinant, soluble fusion protein that is currently under investigation. Atacicept blocks both BLyS and APRIL activity, and it is thought that this dual blockade may lead to a more potent treatment alternative for patients with SLE.[11,12] Phases I, II, and IIb randomized controlled trials have shown evidence of the safety and efficacy of atacicept in healthy volunteers and patients with SLE.[12–15] Atacicept was well-tolerated[13–15] and improved flare rates,[12] time to first flare,[12] SLE Responder Index 4 scores,[13,15] and attainment of treat-to-target end points.[15,16]

The pharmacokinetics (PK) of atacicept have been previously reported in a phase I study in healthy subjects.[14] The current study pooled final datasets from one phase II and one phase IIb clinical trial of atacicept in patients with SLE with the previous phase I study[12–14] in order to: (1) update the PK model of total (i.e., bound and unbound) atacicept after subcutaneous (s.c.) administration in both patients with SLE and healthy volunteers using the previously identified semimechanistic population PK model in healthy volunteers; (2) to identify covariates explaining PK variability, and, in particular, potential differences between healthy volunteers and patients with SLE; and (3) to predict individual subject area under the curve over a dosing interval (AUC_{τ}) estimates for use in an exposure-response analysis.

METHODS

Clinical studies and sample analysis

The present analysis was based on data from three clinical trials of atacicept, corresponding to development phases

I, II, and IIb. Informed consent was obtained from each participant included in the three clinical studies.

In the phase I single-dose, parallel-group study (EMR700461-022), Japanese and White healthy volunteers received a single dose of s.c. atacicept 25, 75, or 150 mg, or matching placebo ($N = 13$, 12, 12, and 15 in the 4 dose groups, respectively). Serum atacicept levels were assessed at 0, 1, 4, 8, 16, 24, 48, 72, 96, 144, 216, 312, 480, 648, 816, and 984 h postdose.[14] The protocol for the phase I study was approved by the Office for Research Ethics Committees Northern Ireland, and the study was conducted in accordance with the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, the European Union Clinical Trial Directive, and all applicable local regulatory requirements.

In the phase II multicenter study (NCT00624338, APRIL-SLE), patients with SLE were administered s.c. atacicept 75 or 150 mg, or placebo bi-weekly for the first 4 weeks of treatment, then once weekly (q.w.) for a total of 52 weeks. The main objective of APRIL-SLE was to evaluate the safety and efficacy of atacicept for the prevention of flares in patients with moderate to severe SLE.[12] Serum atacicept levels were assessed in all subjects during the treatment period, on day 1 (predose) and at weeks 4, 12, 24, and 52 and during follow-up, at 12 weeks post last dose. A subset of 50 subjects per treatment group provided additional samples at weeks 2, 8, 16, and 20. Samples were collected within 6 h before dosing on study day 1 and at the week 4 visit, and within 12 h before dosing at all subsequent visits. The trial protocol for APRIL-SLE, and all substantial amendments, were approved by the relevant institutional review boards or independent ethics committees and by health authorities, according to country-specific laws. The APRIL-SLE trial was conducted in accordance with the protocol, the ICH guideline for GCP and applicable local regulations as well as with the Declaration of Helsinki.

In the phase IIb multicenter study (NCT01972568, ADDRESS II), patients with SLE received s.c. atacicept 75 or 150 mg, or placebo q.w. for 24 weeks. ADDRESS II evaluated the safety and efficacy of atacicept compared with placebo in reducing SLE disease activity in patients with active, autoantibody-positive SLE who were receiving standard of care therapy.[13] The dose–response relationship was also evaluated. Atacicept levels were assessed in all patients during the treatment period, on day 1 (predose) and at weeks 2, 4, 8, 12, 16, 20, and 24 and during follow-up, at weeks 4, 12, and 24 post last dose. In a subset of patients, four additional blood samples were collected for PK analyses at 4 and 24 h post first dose, within 25 h before the second dose, and 24 h post last dose. All samples, except those on study days 1, 2, and 163 were collected within 25 h prior to dosing. The ADDRESS II study was performed in accordance with the Declaration of Helsinki, the ICH Note for Guidance on GCP (ICH Topic E6, 1996), and applicable regulatory requirements. All study sites received approval for the study from their local ethics board.

All the subjects in these three studies who had reliable dosing information and sampling times, and who received at least one dose of atacicept, were included in the analysis. Total atacicept in serum was measured following an acid-dissociation step using a validated enzyme-linked immunosorbent assay (ELISA) method developed by Merck Serono GmbH, Darmstadt, Germany (an affiliate of Merck KGaA, Darmstadt, Germany). Total atacicept included unbound "free" atacicept as well as atacicept bound to BLyS or APRIL. The lower limit of quantification (LLOQ) for total atacicept was 100 ng/mL and the upper limit was 5000 ng/mL. The coefficient of variation was 20% for values below the LLOQ and above the upper limit of quantification.

Postdose concentrations below the limit of quantification did not exceed 2% in the combined three-study data set and were excluded from the present analysis.

Population PK modeling

Modeling methodology

Nonlinear mixed effects modeling was performed with NONMEM version 7.3.0 software with Graphical Interface PDxPOP 5.2 (ICON plc). TIBCO Spotfire S+ 8.2 was used for data manipulation, presentation, and the construction of plots. Some of the graphs were created via Perl-speaks-NONMEM (PsN, version 4.4.8), which was also used to aid the development of the nonlinear mixed effect models using NONMEM. The statistical software R (version 3.2.2), as well as the R package Xpose 4.5.3 was used for the exploratory analysis and post-processing of NONMEM output (e.g., to assess goodness-of-fit). The First Order Conditional Estimation with Interaction estimation method was used.[17,18] Criteria for model selection were based on a likelihood ratio test with $p < 0.01$ for inclusion in the model and $p < 0.001$ for backward elimination.

Goodness-of-fit was assessed by diagnostic plots that included plots of observations versus population and individual predictions; plots of population, individual and conditional weighted residuals versus time and quartile-quartile plots; histograms of individual random effects; and correlations between interindividual random effects, for all the data and also stratified by study, dose, and dosing regimen.

Stability was assessed by successful minimization, including a covariance step, a minimum of three significant

digits for parameter estimation, correlations between parameters less than 0.95 and condition number of the covariance matrix of parameters less than1000.[19]

Model description

A two-compartment quasi-steady-state (QSS) approximation of the target-mediated drug disposition (TMDD) binding model with first-order absorption[20,21] had previously adequately described total atacicept concentrations from the phase I and phase II APRIL-SLE studies.[14,22] This model is shown schematically in Figure S1, together with the differential equations used.

The model was parameterized in terms of absorption rate constant (K_a), nonspecific apparent clearance (CL/F), apparent volume of the central compartment (V_c/F), apparent distributional clearance (Q/F), apparent volume of the peripheral compartment (V_p/F), steady-state constant (K_{ss}), drug-target complex elimination rate constant (K_{int}), target elimination rate constant (K_{deg}), target concentration at baseline (R_{max}) and target production rate (K_{syn}). The K_{syn} was determined as the product of R_{max} and K_{deg}. Interindividual variability (IIV) was tested for all parameters during model development. The Ω matrix elements of the previous model were expanded by including IIV terms for the remaining structural parameters (K_a, Q, K_{ss}, K_{int} and K_{deg}) and a full Ω matrix. This exploration resulted in the inclusion of IIV on K_a. Covariate effects of body weight on CL/F and V_c/F and age on K_a, and separate proportional residual error terms for healthy volunteers and patients with SLE were also included.

Application of the previously developed model to the data set from the three studies

The current analysis represents the second step of a two-step modeling project in which the predictive performance of the previously developed QSS TMDD model[22] was first evaluated externally for the ADDRESS II study data, using confidence interval visual predictive checks (CIVPCs).[23] The model was subsequently updated to include data from the ADDRESS II study.

The previously developed PopPK model was shown to be predictive of the ADDRESS II data and, therefore, the structural part of the model was retained (Figure S2). Previously identified covariate relationships were removed, and base PK model development focused on refining the statistical part of the model. An expansion of the Ω matrix elements was attempted by including IIV terms for the remaining structural parameters (K_a, Q, K_{ss}, K_{int}, and K_{deg}) as well as attempting to implement a full Ω matrix. Inclusion of an additional residual error term for the phase IIb study was also tested.

Identification of covariates was performed using forward selection and backward elimination principles. First, covariates that were significant in the previous model were investigated, including body weight on Q/F and V_p/F. Subsequently, possible covariates on F1 were explored and all other covariates were tested. Finally, a backward elimination step was implemented.

The following covariates, relevant from a biological or pharmacological point of view, were included in the covariate search: weight, age, creatinine clearance, serum BLyS and APRIL (all at baseline), atacicept dose, gender, race, and SLE versus healthy volunteer populations. Initially, covariates included in the previous model were re-introduced. Potential differences in relative bioavailability between healthy volunteers and patients with SLE and between studies were also examined. Because some of the empirical parameter estimates of ETAs appeared to be skewed (variance of random effect of $[\omega^2]V_c$) or associated with high shrinkage ($\omega^2 V_c$, $\omega^2 V_p$, and $\omega^2 K_a$), alternative methods for screening covariates were performed, including a univariate analysis of the remaining covariate effects, followed by forward selection and backward elimination. In addition, the models developed were evaluated internally using CIVPC.

Model-based exposure metrics ([AUC_τ, where $\tau = 168$ h, selected to reflect the proposed q.w. regimen] and maximum concentration [C_{max}]) were derived through simulation of steady-state profiles over a weekly dosing interval, using the individual post hoc parameter estimates and the dose to which each subject was assigned. Atacicept profiles were also simulated for weights corresponding to the minimum (34 kg), first quartile (57 kg), median (65 kg), third quartile (77 kg), and maximum (135 kg) weights of all subjects enrolled in the trials, following the first dose and at steady-state for a q.w. regimen.

RESULTS

Patient characteristics

A total of 540 subjects, contributing a total of 3640 serum atacicept concentration records, were included in the model (7 observations per subject on average). The number of subjects included per study was 37 (533 PK observations), 298 (1728 PK observations), and 205 (1379 PK observations) for the phase I, APRIL-SLE, and ADDRESS II studies, respectively. The SLE population consisted of 503 (93.1%) subjects. Demographic characteristics are shown in Table S1.

Final population PK model

The structural part of the base model of the present analysis was the same as the previous QSS TMDD model.[14,22] An IIV term for the first-order K_a was included, in addition to those for CL/F, V_c/F, V_p/F, and R_{max}, while using a diagonal Ω matrix. The residual error was found to be adequately described by two proportional terms, one for healthy volunteers and one for patients with SLE.

The final model included the previously identified effects of body weight on both CL/F and V_c/F as well as an additional effect of baseline BLyS concentration on R_{max}.

Inclusion of covariates did not appear to greatly affect IIV, with only a 10% reduction (absolute) from the baseline model for V_c and R_{max}. IIV parameters were estimated with very good precision (relative standard errors [RSEs] of 9.2%–18%), whereas RSE for IIV (K_a) was 35%. Residual variability was also estimated precisely, with RSE of 0.9%–2%, and was comparable to the base model. Residual variability was moderate and was slightly higher in patients with SLE than in healthy volunteers, with coefficients of variation of 25% and 19%, respectively.

The model provided precise (RSE of 4.0%–14%) estimates of all structural parameters, including binding (K_{ss}), target turnover (R_{max}, and K_{deg}), and drug-target complex elimination (K_{int}) parameters (Table 1). Total atacicept concentrations in the three trials were adequately

TABLE 1 PK model parameter estimates.

	NONMEM estimates				
Parameter	**Point estimate**	**95% CI**	**% RSE**		
CL/F (L/h)	0.324	0.298–0.350	4.10		
V_c/F (L)	36.3	31.9–40.7	6.14		
Q/F (L/h)	0.149	0.114–0.184	11.9		
V_p/F (L)	38.5	31.0–46.0	9.90		
K_a (h^{-1})	0.0705	0.0595–0.0815	7.94		
K_{ss} (ng/mL)	19.9	14.4–25.4	14.1		
K_{int} (h^{-1})	0.000618	0.000572–0.000664	3.83		
K_{deg} (h^{-1})	0.00362	0.00307–0.00417	7.82		
R_{max} (ng/mL)	715	613–817	7.27		
Weight on CL	0.75 fixed	–	–		
Weight on V_c	1.00 fixed	–	–		
BLyS on R_{max}	0.176	0.120–0.232	16.2		
Interindividual variability	**Point estimate**	**Etabar (SE)**	***p***	**CV%**	**%Shr**
ω^2_{CL}	0.233	−0.017 (0.015)	0.281	48.3	23.0
ω^2_{Vc}	0.284	−0.100 (0.012)	0.000	53.3	48.8
ω^2_{Rmax}	0.102	−0.019 (0.009)	0.035	31.9	32.8
ω^2_{Vp}	0.532	0.014 (0.018)	0.419	72.9	43.3
ω^2_{Ka}	0.182	−0.0002 (0.005)	0.681	42.7	71.7
Residual variability	**Point estimate**	**95% CI**	**%RSE**	**CV%**	**%Shr**
Proportional error no SLE	0.188	0.181–0.195	1.96	18.8	12.0
Proportional error SLE	0.251	0.247–0.255	0.837	25.1	

Note: CV% 100* $\sqrt{\omega^2}$ for log-normally distributed variability terms, Etabar (interindividual random error estimate) is the arithmetic mean of the η (interindividual random error) estimates and the p value for the null hypothesis that the true mean is zero.Abbreviations: BLyS, B cell stimulating factor; CI, confidence interval; CL, clearance; CL/F, total apparent clearance; K_a, absorption rate constant; K_{deg}, target elimination rate constant; K_{int}, drug-target complex elimination rate constant, K_{ss}, steady-state constant; PK, pharmacokinetic; R_{max}, baseline target concentration; Q/F, apparent intercompartmental clearance; %RSE percent relative standard error of the estimate = SE/parameter estimate × 100; Shr, shrinkage; SLE, systemic lupus erythematosus; V_c/F, apparent volume of central compartment, V_p/F, apparent volume of the peripheral compartment, ω^2_{CL}, ω^2_{Vc}, ω^2_{Vp}, ω^2_{Ka} and ω^2_{Rmax} variance of random effect of CL/F, V_c/F, V_p/F, K_a, and R_{max}, respectively.

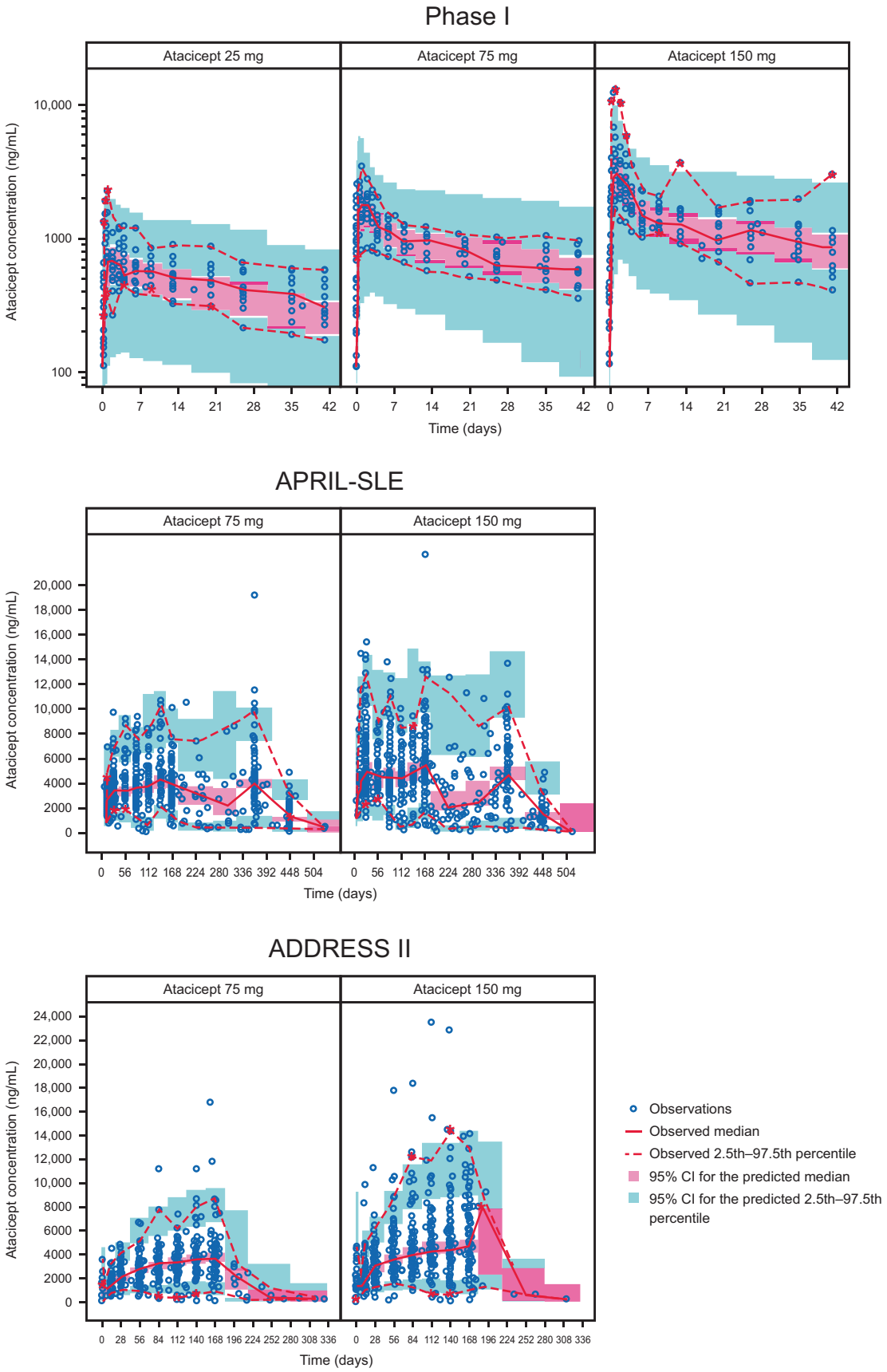

FIGURE 1 CI visual predictive check for the phase I study in healthy volunteers, APRIL-SLE, and ADDRESS II by atacicept dose. Asterisks denote values outside the prediction bounds. The *y* axis scales are different between the studies. APRIL-SLE, a proliferation-inducing ligand-systemic lupus erythematosus; CI, confidence interval.

described, and the model correctly captured the central tendency and variability in the data (Figure 1).

Re-estimation of the parameters of the previously developed QSS TMDD model following the inclusion of the data from ADDRESS II resulted in comparable estimates to those reported previously. Almost all of the structural parameter estimates were within 20% of previous estimates, consistent with the external predictive performance of the previous model. The only parameter estimate that differed by more than 20% following inclusion of the ADDRESS II data was K_{ss}, which was estimated as 37% higher than the previous estimate. The addition of the data from ADDRESS II allowed for the inclusion of an IIV term on K_a, which resulted in the previously identified age effect on K_a being nonsignificant. The additional data also resulted in identification of the positive association between baseline BLyS concentrations and baseline target concentrations.

Effect of covariates

Body weight (on CL/F and V_c/F) and baseline BLyS concentration (on R_{max}) were the only statistically significant covariates identified by the model. Both atacicept CL/F and V_c/F increased with body weight following allometric relationships (exponents fixed to 0.75 and 1.00, respectively). This resulted in a less than 20% difference in atacicept exposure (AUC_τ) for the 10th and the 90th percentiles of body weight, compared with the median (data not shown).

Typical patient profiles of total atacicept following q.w. dosing after first dose and at steady-state simulated at body weight distribution quartiles are presented in Figure 2 and summarized in Table 2. For the range of weights in the analysis, the difference in atacicept exposure was as high as 32% for the minimum or maximum body weight in the population tested, compared with the median (Figure 2, Table 2). The difference in steady-state C_{max} was slightly higher, up to 42%.

Baseline target concentration increased with baseline BLyS (R_{max}~(BLyS [in ng/mL]/2.56)$^{0.176}$). R_{max} was estimated to be 77% higher for the highest baseline BLyS value (39.4 ng/mL) compared with the lowest BLyS value (1.56 ng/mL–the LLOQ). The effect of BLyS on atacicept exposure was also evaluated. The difference in both AUC_τ and steady-state C_{max} was less than 20% for the minimum and the 97.5th percentile of the BLyS distribution of the observed data, compared with the median (Figure 3, Table 3).

The magnitude of the effect of body weight and baseline BLyS on atacicept exposure for the range of the covariates in the present analysis was rather low, with the difference in AUC compared with the median ranging from 20% to 32% for body weight, and 7% to 18% for BLyS.

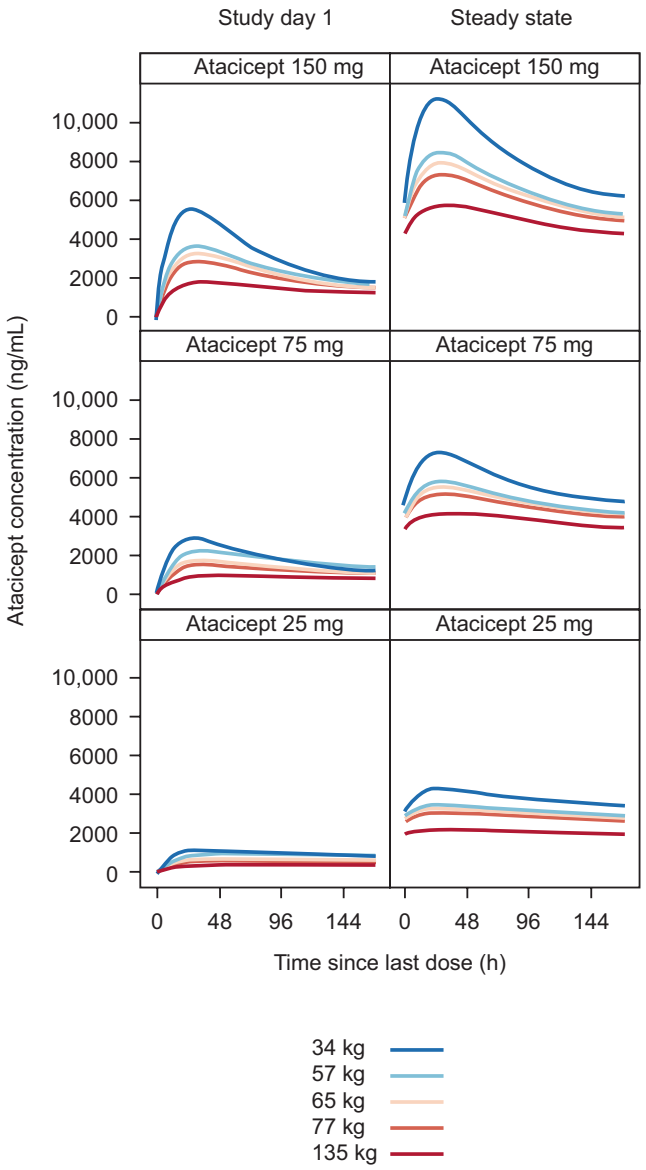

FIGURE 2 Simulated typical subject PK profiles of total atacicept (q.w. dosing) for a range of weights, after the first dose and at steady-state. The curves represent the minimum (34 kg), Q1 (57 kg), median (65 kg), Q3 (77 kg), and maximum (135 kg) body weights used in the simulation. PK, pharmacokinetic; Q, quartile; q.w., once weekly; SD, study day. Note that the minimum weight among all the atacicept-treated patients was 37 kg (Table S1). However, the minimum weight used in the simulations was 34 kg, as this was observed on a placebo-treated patient in a proliferation-inducing ligand-systemic lupus erythematosus (APRIL-SLE); the simulations covered the full range of body weights that were encountered during the trials.

Nevertheless, both covariate effects were retained in the model because they were considered physiologically plausible.

No significant differences in PKs were detected between healthy volunteers and patients with SLE, or between different racial groups.

TABLE 2 Simulated typical patient PK profile summary of total atacicept (q.w. dosing) for a range (minimum, quartiles, and maximum) of weights, after first dose and at steady-state.

Body weight		C_{max} (ng/mL)			AUC_{τ} (10^6 ng/mL h)		
Description	**Weight (kg)**	**25 mg atacicept**	**75 mg atacicept**	**150 mg atacicept**	**25 mg atacicept**	**75 mg atacicept**	**150 mg atacicept**
Week 1							
Min	34	1118	2884	5517	0.152	0.315	0.547
Q1	57	749	1910	3607	0.110	0.238	0.406
Median	65	670	1718	3231	0.100	0.221	0.375
Q3	77	575	1497	2801	0.086	0.199	0.337
Max	135	335	942	1737	0.051	0.138	0.233
Steady-state							
Min	34	4274	7265	11,167	0.640	0.982	1.399
Q1	57	3471	5782	8401	0.538	0.831	1.130
Median	65	3276	5481	7862	0.511	0.798	1.075
Q3	77	3025	5125	7245	0.475	0.758	1.010
Max	135	2191	4126	5670	0.350	0.636	0.837
Absolute and % Δ between minimum and median weights at steady-state		998 (30%)	1784 (33%)	3305 (42%)	0.129 (25%)	0.184 (23%)	0.324 (30%)
Absolute and % Δ between median and maximum weights at steady-state		1085 (33%)	1355 (25%)	2192 (28%)	0.161 (32%)	0.162 (20%)	0.238 (22%)

Note: The shaded boxes show the steady state values for the median weight of 65 kg. Note that the minimum weight among all the atacicept-treated patients was 37 kg (Table S1). However, the minimum weight used in the simulations was 34 kg, as this was observed on a placebo-treated patient in APRIL-SLE; the simulations covered the full range of body weights that were encountered during the trials.

Abbreviations: AUC_{τ}, area under the concentration–time curve for the dosing interval; C_{max}, maximum concentration; max, maximum; min, minimum; PK, pharmacokinetic; Q, quartile; QW, once weekly; Δ, difference.

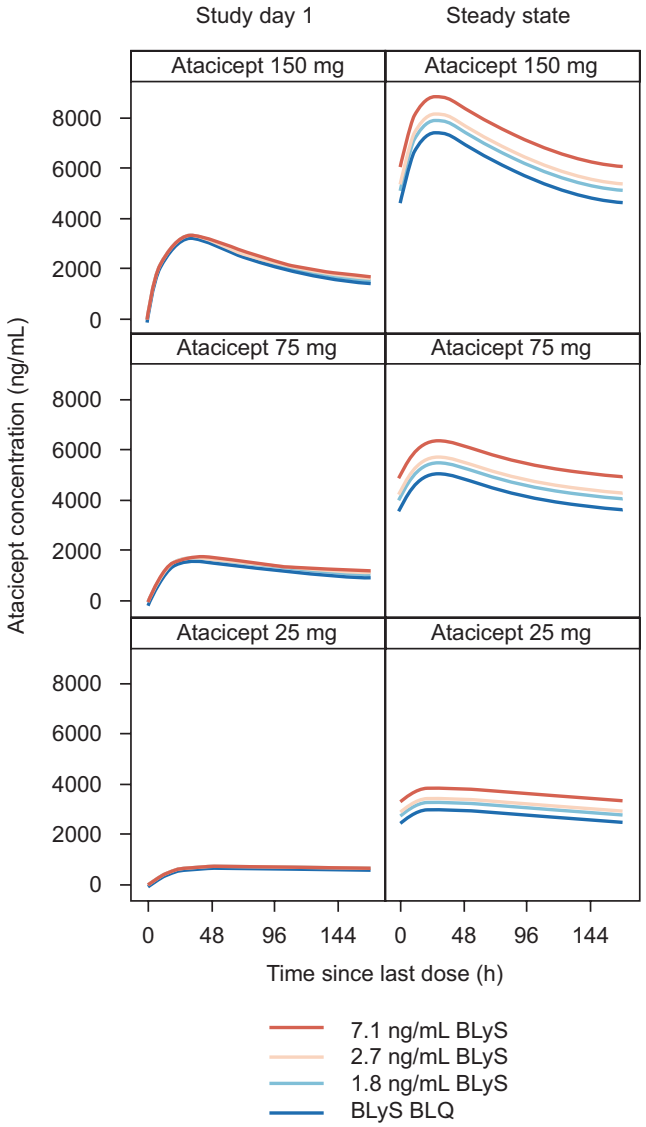

FIGURE 3 Simulated typical subject PK profiles of total atacicept for a range of baseline BLyS concentrations after first dose and at steady-state with once weekly dosing. The curves represent the minimum and Q1 (values below the limit of quantification), median (1.8 ng/mL), Q3 (2.7 ng/mL), and the 97.5th (7.1 ng/mL) percentile values used in the simulation. BLQ, below limit of quantitation; BLyS, B cell stimulating factor; PK, pharmacokinetic; *Q*, quartile; SD, study day.

DISCUSSION

In this population PK analysis, a QSS TMDD population PK model for total atacicept concentrations (free and bound to BLyS and/or APRIL) was developed using pooled final datasets from three studies: a phase I study in healthy subjects,[14] and two phase II studies in patients with SLE (i.e., the APRIL-SLE [phase II][12] and ADDRESS II [phase IIb][13] studies.

PK analyses of atacicept serum levels have already been carried out in clinical studies assessing single- and multiple-dose regimens of atacicept in healthy volunteers,[24] and patients with SLE,[25–27] rheumatoid arthritis,[28] multiple sclerosis, non-Hodgkin's lymphoma,[29] and multiple myeloma and active Waldenström's macroglobulinemia.[30] The PK profiling of single s.c. doses of atacicept in the healthy volunteer first-in-human study covered a broad dose range, namely from 2.1 to 630 mg atacicept.[24] However, PK data from these studies were derived using a previously validated ELISA, which was subsequently found to have inadequacies linked to the bioanalytical reference standard. Hence, this population PK analysis includes only PK data based on the new developed and validated bioanalytical ELISA for total atacicept, although this meant that the model was built on data from limited dose levels, a potential limitation.

The starting point of the present analysis was the two-compartment QSS TMDD model with first-order absorption that was previously developed for atacicept using data from the phase I study and APRIL-SLE. This type of TMDD model is adapted to large proteins with high affinity for their receptors, independent of SLE pathology. The QSS approximation, as opposed to the full TMDD, was required because only the total concentrations were measured whereas the full TMDD model requires both free and total concentration measurements to be identified.[20,21] In addition, the assumption for QSS approximation states that it produces very similar results to the full TMDD model if the binding, dissociation, and elimination of the complex occur rapidly relative to other processes, which is expected for atacicept.

The external predictivity of this model was demonstrated using the data from ADDRESS II, confirming the consistency of the data from this study with the previous data. As a result, no changes to the structural model were made during the analysis. Refinement of the model focused only on exploring the possible inclusion of additional IIV and residual variability terms and the covariate analysis. This included the expansion of the Ω matrix elements by including IIV terms for the remaining structural parameters (K_a, Q, K_{ss}, K_{int}, and K_{deg}) and a full Ω matrix. This exploration resulted in the inclusion of IIV on K_a. Two proportional residual error terms, one for healthy volunteers and one for patients with SLE, were already included in the model. Inclusion of an additional proportional error term for ADDRESS II and an additive error term did not improve the model. Using the same error term for both healthy volunteers and patients resulted in worse model fit; therefore, the original residual error structure of the model was retained.

One additional IIV term (on K_a) was included in the final model of the present analysis, compared with the previously developed model. The addition of IIV on K_a may explain why the previously identified effect of age on K_a was not found to be significant in the present

TABLE 3 Simulated typical subject PK profiles of total atacicept (q.w. dosing) for a range of baseline BLyS concentrations after first dose and at steady-state.

BLyS		C_{max} (ng/mL)			AUC_τ (10^6ng/mLh)		
Description	Concentration (ng/mL)	25 mg atacicept	75 mg atacicept	150 mg atacicept	25 mg atacicept	75 mg atacicept	150 mg atacicept
Week 1							
Min and Q1	BLOQ	656	1689	3202	0.096	0.212	0.365
Median	1.8	670	1718	3231	0.100	0.221	0.375
Q3	2.7	676	1733	3247	0.101	0.225	0.380
97.5th percentile[a]	7.1	686	1774	3289	0.103	0.238	0.394
Steady-state							
Min and Q1	BLOQ	2972	5039	7388	0.460	0.724	0.995
Median	1.8	3276	5481	7862	0.511	0.798	1.075
Q3	2.7	3434	5718	8118	0.538	0.838	1.118
97.5th percentile[a]	7.1	3835	6352	8806	0.605	0.945	1.233
Absolute and % Δ between min and median BLyS at steady-state		304 (9%)	442 (8%)	474 (6%)	0.051 (10%)	0.074 (9%)	0.080 (7%)
Absolute and % Δ between median and 97.5th percentile BLys at steady-state		559 (17%)	871 (16%)	944 (12%)	0.094 (18%)	0.147 (18%)	0.158 (15%)

Note: The shaded boxes show the steady-state values for the median concentration of 1.8 (ng/mL).

Abbreviations: AUC_τ, area under the concentration–time curve for the dosing interval; BLOQ, below the limit of quantification; BLyS, B cell stimulating factor; C_{max}, maximum concentration; max, maximum; min, minimum; PK, pharmacokinetic; *Q*, quartile.

[a]The 97.5th percentile was used because the maximum was a clear outlier.

analysis. The previously identified allometric relationships of CL/F and V_c/F with body weight were retained in the final model. In addition, it was possible to characterize the physiologically relevant positive association between baseline BLyS concentration and R_{max}. A slightly higher residual variability was estimated for patients with SLE, compared with healthy volunteers. Thus, the PK of total atacicept in healthy subjects and patients with SLE were adequately described by the nonlinear two-compartment QSS TMDD binding model with first-order absorption.

Whereas both CL/F and V_c/F were found to increase with body weight and R_{max} to increase with baseline BLyS, the magnitude of the effect of body weight and baseline BLyS on atacicept exposure was low, with the difference in AUC_τ compared with the median of 20%–32% for body weight, and 7%–18% for BLyS. Therefore, the effects of these covariates on atacicept exposure are not expected to be of clinical relevance. Furthermore, the PKs of atacicept did not differ significantly between healthy volunteers and patients with SLE, or between different racial groups. Immunogenicity was not included as a potential covariate as few patients in the trials developed antibodies to atacicept.[12–14]

Whereas the total (complexed and unbound) atacicept in human serum measured by ELISA was used to build the population PK model described here, a second potential limitation of this model is that "free" (unbound) atacicept and atacicept–BLyS/APRIL complex data were not included. Consequently, this model has been further extended to estimate free (unbound) atacicept concentrations,[31] considering that only free (unbound) drug represents the pharmacologically active fraction exerting a therapeutic effect.[32] It was important to assess whether the kinetics of the "free" atacicept predicted from the population PK model was comparable with the "active" atacicept concentrations experimentally determined using a sensitive functional reporter cell assay. Of note, experimentally determined kinetics of "active" atacicept concentrations using a functional reporter cell assay[33] mirrored the population PK-derived "free" atacicept kinetic profiles and provided additional support for the q.w. dosing regimen used in clinical development of atacicept.[31]

Atacicept is being studied for use in SLE because it binds to both the BLyS and APRIL B cell activating factors, whereas belimumab (a currently approved monoclonal antibody therapy) is directed against BLyS only. Furthermore, the receptors for BLyS and APRIL are expressed differentially on B cells according to their developmental stage, which suggests that different proposed B cell-directed therapies may differ in regard to their relative risks and benefits.[25]

Regarding efficacy, both phase II clinical trials (APRIL-SLE and ADDRESS II) demonstrated that atacicept reduces clinical end points in SLE.[12,13,15] Exposure measures obtained using the population PK model were used to develop exposure–response models based on data from the APRIL-SLE and ADDRESS II studies, which showed that the optimal atacicept exposure for efficacy appeared to be a steady-state $AUC_\tau \geq \sim 1 \times 10^6$ ng/mL* h.[34] In the current study, simulated typical patient profiles over a range of body weights and baseline BLyS concentrations showed steady-state values of around 1×10^6 ng/mL *h with atacicept 150 mg q.w., thus supporting the selection of this dose regimen for patients with SLE in phase III studies.

Regarding safety, any new treatment that affects B cells must be monitored for the possibility of a reduced immune response and/or an increased risk of infection. During APRIL-SLE, two deaths were reported in the atacicept 150 mg treatment arm, which was terminated as a precautionary measure.[12] A similar number of deaths had been reported in other large clinical trials of new therapies in SLE.[8,35–37] Several additional risk-mitigation measures were implemented in ADDRESS II, which may have minimized the risk of serious infections and no deaths were reported.[13]

The population PK model is mechanistically sound, with its basic structure externally evaluated, and was able to correctly capture the central tendency and variability in the data. Potential limitations of this study include the relatively short treatment period in ADDRESS II (24 weeks) and the early termination of the 150 mg arm in APRIL-SLE, which led to a lower number of patients in the 150 mg group completing the 52-week treatment period than the 75 mg group.

CONCLUSIONS

The PKs of atacicept in healthy subjects and patients with SLE were adequately described by a nonlinear two-compartment QSS TMDD binding model with first-order absorption, without any differences found between the two populations. The population PK model allowed the simulation of the complete total atacicept concentration–time profile in patients with SLE, contributing to the identification of exposure–response relationships for pharmacodynamic, clinical, and safety end points. These findings provide a data-driven foundation for atacicept dose selection for further clinical trials.

AUTHOR CONTRIBUTIONS

M.P., Ö.Y., C.F., P.G., C.V.-M., and O.P. wrote the manuscript. O.P. designed the research. M.P., C.F., P.G., and O.P. performed the research. O.P., M.P., and C.F. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

M.P. and C.F. are employees of ICON Clinical Research UK Ltd, Marlow, UK; ICON received professional fees for performing the analysis. Ö.Y. was an employee of the healthcare business of Merck KGaA, Darmstadt, Germany, when the study was conducted. P.G. and O.P. are employees of Merck Institute for Pharmacometrics, Lausanne, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany. C.V.-M. is an employee of EMD Serono, Billerica, MA, USA.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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